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Possible New Variant of Nijmegen Breakage Syndrome

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We report on a child with microcephaly, small facial and body size, and immune deficiency. The phenotype is consistent with Nijmegen breakage syndrome (NBS), with additional clinical manifestations and laboratory findings not reported heretofore. Most investigations, including the results of radiation-resistant DNA synthesis, concurred with the diagnosis of NBS. Cytogenetic analysis documented abnormalities in virtually all cells examined. Along with the high frequency of breaks and rearrangements of chromosomes 7 and 14, we found breakage and monosomies involving numerous other chromosomes. Because of some variation in the clinical presentation and some unusual cytogenetic findings, we suggest that our patient may represent a new variant of Nijmegen breakage syndrome.

KEY WORDS: Nijmegen breakage syndrome, chromosome breaks, radioresistant DNA synthesis, microcephaly, cancer

INTRODUCTION

Nijmegen breakage syndrome (NBS) is an autosomal recessive chromosome instability disorder of microcephaly, short stature, peculiar facial appearance, and immunological defects involving both the humoral and the cellular systems. Chromosomal anomalies consist of random breaks and rearrangements, involving mainly chromosomes 7 and/or 14 in lymphocytes [Weemaes et al., 1981; Taalman et al., 1989; Barbi et al., 1991]. DNA synthesis in cultured lymphocytes and fibroblasts of these patients is more resistant to γ-irradiation than that of controls [Taalman et al., 1983].

We describe a new patient with certain physical findings, not present in other reported cases with chromosomal breakage, involving mostly chromosomes 7 and 14 in lymphocytes and a high frequency of apparently random monosomies.

CLINICAL REPORT

T.G., a 5-year-old boy, was born after an uneventful pregnancy to primigravid nonconsanguineous parents of Yugoslavian/Hungarian and American/English descent. The mother's maternal grandmother had breast cancer. Both parents were 29 years old at the time of his birth. The delivery was at 34½ weeks of gestation by cesarean section for intrauterine growth retardation. Birth weight was 1,860 g, length was 43 cm, and birth occipito-frontal circumference (OFC) was 27.7 cm, all considerably below the 3rd centile. He had a peculiar face with sloping forehead, broad nasal bridge, anteverted nostrils, micrognathia (Figs. 1, 2), left single palmar crease, clinodactyly of the left fifth finger with a single interphalangeal crease, partial syndactyly of the right second and third toes, with mild hypoplasia of the third toe, and penoscrotal hypospadias with descended testes (Fig. 3). There was no hyper- or hypopigmentation of the skin.

CT scan of the brain demonstrated schizencephaly. Serum α-fetoprotein (AFP) at age 16 months was normal (5.9 μg/l). Immunoglobulin and complement were normal. Blood IgE was absent; the other immunoglobulin and complement results were as follows: IgG: 4.99 g/l; IgM: 1.02 g/l; IgA: 1.53 g/l; C3: 0.70 g/l; and C4: 0.31 g/l. T.G.'s immune deficiency was characterized by a profound lymphopenia and depressed T- and B-cell populations. The lymphopenia affected both the CD4 (helper T

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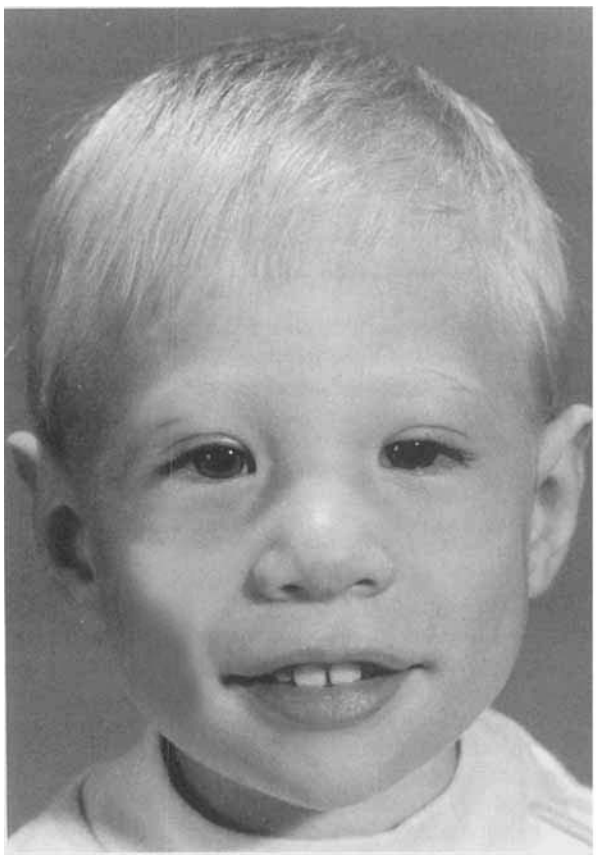

Fig. 1. Face of patient T.G. at age 21 months.

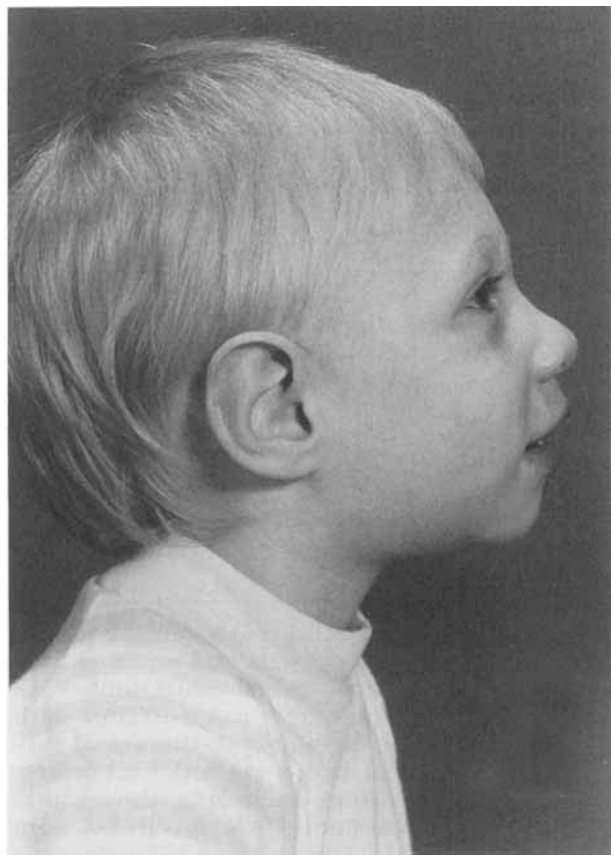

Fig. 2. Profile of patient T.G. at age 21 months.

cell) and CD8 (suppressor T cell) subsets, but his CD4/CD8 ratio was normal (Table I). The lymphocyte stimulation test was performed as follows: T-lymphocytes (2.5×10^5/ml) were cultured in 96-well plates with appropriate dilutions of mitogens, including phytohemagglutinin (PHA), concanavalin A (CON A), and pokeweed mitogen (PWM) in a humidified incubator at 37°C, 7% CO_2 for 72 hr according to standard protocols [Harbeck and Giclas, 1991]. The cells were pulsed with tritiated thymidine 6 hr before harvesting, and harvested by water lysis using a Skatron cell harvester (Skatron, Columbia, MD), and counted by liquid scintillation counting [Mazer et al., 1990]. The response to lymphocyte stimulation by mitogens was very low (Table II). In spite of poor in vitro T-cell function, responses to diphtheria and tetanus vaccines were normal.

The child's development during the first year was normal. He smiled at 2 months, rolled over at 4 months, sat without support at 6½ months, and stood and walked without support at 11 months. No ataxia was noted. His speech was delayed. At age 2⁹⁄₁₂ years he spoke 10 words. At 3⁹⁄₁₂ years he had more than 200 words in his vocabulary and made sentences, but tended to be echolalic. He was also found to be globally delayed, and persistent and oppositional, with a short attention span.

At age 2 years he had a skin eruption. Skin biopsy showed perivascular and perifollicular lymphohistiocytic infiltrates with focal "loose" nonnecrotic granulomata and numerous plasma cells. He was treated conservatively and recovered.

After age 2 years, he had several episodes of respiratory and mucocutaneous infections, most probably of viral origin. HIV antibody test was negative. No bacterial source could be identified. Bone-marrow aspirate documented a decrease in erythropoiesis and mild dyshematopoiesis, but ruled out leukemia or lymphomatas involvement.

At age 4 years, he presented with a left perineal swelling initially considered to be a hematoma secondary to trauma. However, on ultrasonographic and subsequent CT scan examinations and surgery, this was found to be a rhabdomyosarcoma (mainly alveolar type). The surgical margins contained tumor cells, but no metastases were found on evaluation.

Because of the known hypersensitivity of patients with NBS and other chromosome-breakage syndromes to chemotherapy and radiotherapy, our patient was treated with a modified regimen of low doses of actinomycin and cyclophosphamide. He also received a full dose of vincristine and prophylactic intravenous immunoglobulin. He became neutropenic at day 6 despite the reduced doses. Following the second course, he received granulocyte-colony-stimulating factor (G-CSF). He is currently (10 weeks after last chemotherapy) clinically and radiologically free of disease.

Fig. 3. Genitalia of patient T.G. at age 21 months. Note penoscrotal hypospadias.

Cytogenetic Studies

Chromosome analysis was performed six times from blood and three times from fibroblasts established from a skin biopsy. G-banded chromosomes were obtained according to classical techniques. Blood karyotyping after PHA stimulation was successful in 3 out of 6 attempts. A very high rate of chromosome breaks was apparent at the first test, and led to suspicion of NBS. All karyotyped cells showed at least one structural or numerical abnormality. No instability of the centromere heterochromatin was seen.

The number of chromatid or chromosome breaks per karyotyped blood cell was 2.7. Four triradial figures were seen. Monosomies for one or more chromosomes were also observed in 16 of 25 cells. Reciprocal translocations, deletions, and a pericentric inversion of chromosome 7 were seen in 18 cells. Overall, eight cells showed an abnormality of chromosomes 7 and/or 14. Three different marker chromosomes were also observed. A sister chromatid exchange (SCE) study from lymphocytes, using bromo-deoxyuridine (BrdU), gave normal results.

TABLE I. Lymphocyte Subsets

	Percentages	N	Absolute counts
CD 3 (total T cells)	38%	61–77	0.190×10^9/l
CD 19 (total B cells)	6%	13–36	0.030×10^9/l
CD 4 (T helper)	20%	33–51	0.100×10^9/l
CD 8 (T suppressor cells)	18%	21–34	0.090×10^9/l
CD 16/56 (natural killer cells)	39%	<11%	0.195×10^9/l
CD 4/CD 8 ratio	1.1	1.0–2.1	

TABLE II. Lymphocyte Stimulation by Mitogens

	Patient		Control	
Mitogen	cpm	SI	cpm	SI
Unstimulated	1,100		1,666	
PHA	4,400	4.00	312,233	187.42
CON A	3,600	3.27	381,033	228.71
PWM	3,700	3.36	640,950	38.99

Similar chromosomal abnormalities were observed in the fibroblasts (19 cells karyotyped). Chromosome breakage occurred at the rate of 1.26 breaks/cell. Monosomies were present in more than half the cells (Table III). Random structural anomalies and marker chromosomes were also seen. Although chromosome 7 was not involved in rearrangements in karyotyped cells, three cells showed an abnormality involving chromosome 14 (one tandem translocation, one translocation (Y;14), and one deletion). Only one cell had a normal 46,XY karyotype (Table IV).

A diepoxybutane (DEB)-induced chromosome breakage test performed on fibroblasts was within normal limits [Auerbach and Wolman, 1976].

DNA Studies

The results of DNA synthesis measurements in cultured fibroblasts after γ-irradiation [Taalman et al., 1983] are described in Table V. On the basis of clinical and laboratory findings, the diagnosis of NBS was made.

A second pregnancy was tested by amniocentesis, according to the reports of Jaspers et al. [1990] and

TABLE III. Overall Detected Monosomies*

Chromosome	Number of monosomic cells
2	1
3	2
5	1
6	1
7	1
10	2
12	1
13	3
14	1
15	1
16	2
18	2
19	2
21	5
22	4
X	1
Y	2

*Skin fibroblasts and blood.

TABLE IV. Cytogenetic Studies

Cells	Lymphocytes n	Lymphocytes Per cell	Skin fibroblasts n	Skin fibroblasts Per cell
Karyotypes	28		19	
Chromatid breaks	26	0.93	1	0.53
Chromosome breaks	49	1.75	23	1.21
Triradials	4	0.14		
Total rearrangements	26	0.93	17	0.89
Rearrangements involving chromosomes 7 and/or 14	8	0.29	3	0.16
Monosomies	16	0.57	11	0.58

TABLE VI. DNA Synthesis After γ-Irradiation on Amniocytes

	DNA-synthesis after γ-irradiation, % of unirradiated cells 10	15	20	Gy
Amniocytes from patient T.G.'s mother	67	49	46	
Control 1 (normal amniocytes)	66	49	44	
Control 2 (normal amniocytes)	51	40	38	
Fibroblasts from T.G.	79	61	58	
Control (normal fibroblasts)	44	34	32	

Kleijer et al. [1994]. The results were normal (Table VI). A baby girl was born early in 1992. She is physically and developmentally completely normal.

DISCUSSION

Nijmegen breakage syndrome (NBS) shares several important manifestations with ataxia-telangiectasia (AT) [Hecht et al., 1966], Fanconi anemia (FA) [Schroeder et al., 1964], and Bloom syndrome (BS) [Bloom, 1966]. All four conditions are autosomal-recessive disorders with some clinical overlap, chromosomal anomalies, and a predisposition to cancer.

TABLE V. DNA Synthesis After γ-Irradiation

Fibroblasts	DNA synthesis after γ-irradiation, % relative to unirradiated 10	15	20	Gy
T.G. (patient 91RD242)	83	79	72	
A.T. (patient)	81	73	72	
Control	55	45	40	

To date, several patients have been published with many of the physical and laboratory findings of NBS [Hustinx et al., 1979; Weemaes et al., 1981; Taalman et al., 1983, 1989; Byrne et al., 1984; Seemanová et al., 1985; Conley et al., 1986; Maraschio et al., 1986; Wegner et al., 1988; Curry et al., 1989; Barbi et al., 1991; Chrzanowska et al., 1995] (Table VII).

In our patient, FA was ruled out by the DEB test [Auerbach et al., 1989; Giampietro et al., 1993], and BS by the test for sister chromatid exchanges (SCE).

Features common to NBS and AT are immunodeficiency, chromosome rearrangements primarily involving chromosomes 7 and 14 in lymphocytes, increased risk of cancer, and radiation sensitivity, as well as resistance to a decrease in rate of DNA synthesis following ionizing irradiation. Patients with NBS have microcephaly and usually are mentally retarded. However, they do not exhibit the neurocutaneous signs of AT such as ataxia, oculocutaneous telangiectasia, or progeroid skin changes, nor an increase in serum α-fetoprotein level.

TABLE VII. Summary of NBS Patients*

	Weemaes et al., 1981	Seemanová et al., 1985	Maraschio et al., 1986	Conley et al., 1986	Maserati et al., 1988	Wegner et al., 1988	Taalman et al., 1989	Curry et al., 1989	Barbi et al., 1989	Stoppa-Lyonet. et al., 1992
Number of patients	2	9	1	1	2	2	1	Twins	1	1
Sex	M M	5 F, 4 M	F	F	F F	F F	M	F F	F	M
Age (years)	9 6		31	21	11 9	15 7		13 13	46 months	14
Ethnicity	Dutch	Czech	Italian	Eastern European	Italian	German?	Dutch	Mexican	German	Eastern European
Ataxia	– –	–	–	–	+ +	– –	–	+ +	–	–
Telangiectasis	– –	–	–	–	– –	– –	–	– –	–	–
High serum AFP	–	N in 3 living	–	–	– –		–	+ +	↑ 5 months N 2 years	–
Developmental retardation	+ +	–	–	+	+ +	–	+	+ +	Slight	+
Microcephaly	+ +	+	+	+		+ +	+	+ +	+	+
Short stature	+ +		+	+			+	+ +	+	+
Malignancy	+ –	4/9	+	–		+		– –	–	–
Chromosomal instability	+ +	±	+	+	+ +	+ +	+	+ +	+	+
RDS	+	+ in 3 living					+	+ +	+	
Immunodeficiency	Esp. IgA deficiency		+	+	Selective IgE deficiency	+	+	± ±	–	+

*N, normal.

Immunodeficiency in these two conditions demonstrates a spectrum of severity and often consists of IgA, IgE, IgG2, and IgG4 deficiency, and an impaired T-cell responsiveness [Weemaes et al., 1993]. Our patient had profound lymphopenia and depressed T- and B-cell populations. However, he consistently had normal immunoglobulin levels and responded adequately to protein vaccines.

In AT and NBS, patients' culture yield after PHA stimulation is generally poor. Our patient was no exception, as 3 blood cultures out of 6, in two different laboratories, were unsuccessful. A specific chromosome instability is found in AT, consisting of a high frequency of spontaneous chromosomal breaks and rearrangements. A similar pattern of chromosomal anomalies is found in NBS. Triradial figures found in our patient's lymphocytes have already been reported in NBS by Weemaes et al. [1981], but are not a usual finding in AT.

The chromosome rearrangements, including translocations, deletions, inversions, and rearrangements involving chromosome 7 and/or 14, have been described in NBS. The latter are specific to lymphocyte cultures, with preferential breakpoints at 7p12, 7p13, 7q32, 7q34, 7q35, 7q36, 14q11, 14q12, and 14q32 [Taalman et al., 1989; Barbi et al., 1991]. Loci of immunoglobulin chains H, K, and L, and T-lymphocytes receptors TCR G, B, and A/D, are known to map to some of these breakpoints [Aurias, 1994]. It has been suggested that the origin of such chromosome 7 and 14 rearrangements might be the consequence of erroneous recombination involving T- and B-cell genes [Fiorelli et al., 1985; Dewald et al., 1986; Hecht et al., 1986; Scheres et al., 1980]. In a case reported by Stoppa-Lyonnet et al. [1992], chromosomal analysis detected, in addition to the specific aberrations, two clonal T-cell populations not involving the usual bands 14q11.2 and 14q32.1.

In our patient's lymphocytes, as in other NBS patients, we found a higher frequency of rearrangements involving chromosomes 7 and/or 14, with the usual breakpoints at 7p13, 7q36, and 14q11. The translocation points most frequently involved in the chromosome 7 and 14 rearrangements in NBS are the same as those in AT, but the frequencies of involvement of the individual sites are different [Taalman et al., 1989]. As in other reports [Weemaes et al., 1981; Maraschio et al., 1986; Curry et al., 1989], we did not find in fibroblast cultures a preferential involvement of chromosomes 7 and 14 in rearrangements.

In our patient, monosomies were frequent; this is not a common finding in NBS. To our knowledge, they have been mentioned only by Ying and Decoteau [1981]. However, their patient did not have the characteristic findings of NBS.

Cultured cells from patients with AT or NBS demonstrate radioresistant DNA synthesis (RDS) as compared to normal cells. Six different genetic complementation groups were identified based on this test. Two of these, V1 and V2, were NBS patients [Jaspers et al., 1988].

Based on increased chromosomal breakage, increased RDS, and normal levels of serum AFP, our patient was diagnosed as having NBS. Unfortunately, further characterization of this diagnosis by complementation studies using fibroblasts could not be performed.

Woods et al. [1995] reported a 17-month-old male patient of Yugoslavian/Albanian descent. He was diagnosed as having Seckel syndrome but seemed to have physical and chromosomal findings compatible with the diagnosis of NBS. Moreover, this patient had hypospadias, which has been reported in AT, but not in NBS. However, no test measuring rate of DNA synthesis after γ-irradiation was reported. We thus suggest that T.G., and probably the patient of Woods et al. [1995], suffer from a new variant of NBS with a specific phenotype, including the hypospadias.

TABLE VII. Summary of NBS Patients (*continued*)

					Chrzanowska et al., 1995						Present report
M	F	M	M	M	11 F	M	F	M	M	M	1 M
3 $^{10}/_{12}$	13 $^{7}/_{12}$	10 $^{5}/_{12}$	15 $^{10}/_{12}$	11 $^{6}/_{12}$	5 $^{7}/_{12}$ Polish	$^{3}/_{12}$	3 $^{3}/_{12}$	6 $^{8}/_{12}$	$^{3}/_{12}$	10 $^{7}/_{12}$	5 Yugo/ English
–	–	–	–	–	–	–	–	–	–	–	–
+	+	+	–	–	+	–	–	–	–	+	–
–	–	–	–	–	–	+/–	–	–	–	–	–
					50% low normal intelligence-borderline mental retardation; 50% mild-to-moderate mental retardation						+
+	+	+	+	+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+	+	+	+	+
–	+ B cell lymphoma	–	–	–	–	–	–	–	–	–	+
+	+	+	+	+	+	+	+	+	+	+	+
+	+	+	+	+	+	NA	NA	NA	+	+	+
+	+	+	+	+	+	+	+	+	+	+	+

The malignancies in NBS and AT are usually of lymphoid origin (non-Hodgkin's lymphomas, leukemia) [Ying and Decoteau, 1981; Seemanová et al., 1985; Maraschio et al., 1986; Wegner et al., 1988; Filipovich et al., 1987; Chrzanowska et al., 1995]. The chromosomal breaks may be a predisposing factor to malignancies. Our patient developed a rhabdomyosarcoma. This is the most common soft-tissue sarcoma in persons under age 21, and accounts for 5–8% of all cases of childhood cancer [Kramer et al., 1983]. To our knowledge, rhabdomyosarcomas have not been previously reported in patients with NBS.

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